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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<p>(51) International Patent Classification <sup>5</sup> : C07D 401/12, A61K 31/44</p>	<p>A1</p>	<p>(11) International Publication Number: WO 94/27988 (43) International Publication Date: 8 December 1994 (08.12.94)</p>
<p>(21) International Application Number: PCT/SE94/00509 (22) International Filing Date: 27 May 1994 (27.05.94) (30) Priority Data: 9301830-7 28 May 1993 (28.05.93) SE (71) Applicant (for all designated States except US): ASTRA AKTIEBOLAG [SE/SE]; S-151 85 Södertälje (SE). (72) Inventors; and (75) Inventors/Applicants (for US only): LINDBERG, Per, Lennart [SE/SE]; Gundas Gata 40, S-431 51 Mölndal (SE). VON UNGE, Sverker [SE/SE]; Alvågen 4, S-430 33 Fjärås (SE). (74) Agent: LARSSON, Birgitta; AB Astra, Patent Dept., S-151 85 Södertälje (SE).</p>		<p>(81) Designated States: AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, ES, FI, GB, GE, HU, JP, KG, KP, KR, KZ, LK, LU, LV, MD, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TJ, TT, UA, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).  Published With international search report.</p>
<p>(54) Title: OPTICALLY PURE SALTS OF PYRIDINYLMETHYL SULFINYL-1H-BENZIMIDAZOLE COMPOUNDS (57) Abstract  The novel optically pure compounds Na<sup>+</sup>, Mg<sup>2+</sup>, Li<sup>+</sup>, K<sup>+</sup>, Ca<sup>2+</sup> and N<sup>+</sup>(R)<sub>4</sub> salts of (+)-5-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole or (-)-5-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole, where R is an alkyl with 1-4 carbon atoms, processes for the preparation thereof and pharmaceutical preparations containing the compounds as active ingredients, as well as the use of the compounds in pharmaceutical preparations and intermediates obtained by preparing the compounds.</p>		

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Optically pure salts of pyridinylmethyl sulfinyl-1H-benzimidazole compounds.

Field of the invention

- 5 The present invention is directed to new compounds with high optical purity, their use in medicine, a process for their preparation and their use in the manufacture of pharmaceutical preparation. The invention also relates to novel intermediates in the preparation of the compounds of the invention.

10 Background of the invention

- The compound 5-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole, having the generic name omeprazole, and therapeutically acceptable alkaline salts thereof are described in EP 5129 and  
15 EP 124 495, respectively. Omeprazole and its alkaline salts are effective gastric acid secretion inhibitors, and are useful as antiulcer agents. The compounds, being sulfoxides, have an asymmetric center in the sulfur atom, i.e. exist as two optical isomers (enantiomers). It is desirable to obtain compounds with improved pharmacokinetic and metabolic properties which will give an improved therapeutic  
20 profile such as a lower degree of interindividual variation. The present invention provides such compounds, which are novel salts of single enantiomers of omeprazole.

- The separation of the enantiomers of omeprazole in analytical scale is described in  
25 e.g. J. Chromatography, 532 (1990), 305-19 and in a preparative scale in DE 4035455. The latter has been done by using a diastereomeric ether which is separated and thereafter hydrolysed in an acidic solution. Under the acidic conditions needed for hydrolysis of the attached group, omeprazole is quite sensitive and the acid has to be quickly neutralized with a base to avoid  
30 degradation of the acid-sensitive compound. In the above mentioned application

this is done by adding the reaction mixture containing concentrated sulfuric acid to a concentrated solution of NaOH. This is disadvantageous because there is a great risk of locally reaching pH values between 1-6, which would be devastating for the substance. Moreover, instantaneous neutralisation will create heat which will be  
5 difficult to handle in large scale production.

The present invention in a further aspect provides a novel method for preparing the novel compounds of the invention in large scale. This novel method can also be used in large scale to obtain single enantiomers of omeprazole in neutral form.  
10

There is no example known in the prior art of any isolated or characterized salt of optically pure omeprazole, i.e. single enantiomers of omeprazole neither of any isolated or characterized salt of any optically pure omeprazole analogue.

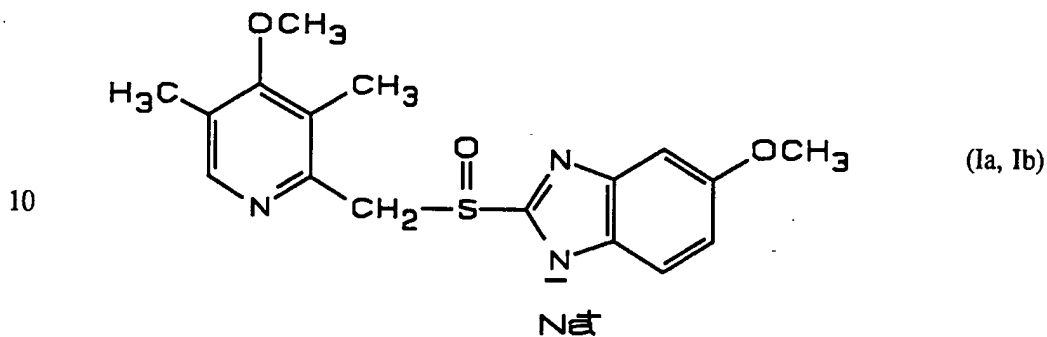
15 Detailed description of the invention

The present invention refers to the new  $\text{Na}^+$ ,  $\text{Mg}^{2+}$ ,  $\text{Li}^+$ ,  $\text{K}^+$ ,  $\text{Ca}^{2+}$  and  $\text{N}^+(\text{R})_4$  salts of the single enantiomers of omeprazole, where R is an alkyl with 1-4 carbon atoms, i.e.  $\text{Na}^+$ ,  $\text{Mg}^{2+}$ ,  $\text{Li}^+$ ,  $\text{K}^+$ ,  $\text{Ca}^{2+}$  and  $\text{N}^+(\text{R})_4$  salts of (+)-5-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole and  
20 (-)-5-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole, where R is an alkyl with 1-4 carbon atoms.

Particularly preferred salts according to the invention are the  $\text{Na}^+$ ,  $\text{Ca}^{2+}$  and  $\text{Mg}^{2+}$  salts, i.e. (+)-5-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole sodium salt, (-)-5-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole sodium salt, (+)-5-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole magnesium salt, (-)-5-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole magnesium salt, (+)-5-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-  
25  
30

pyridinyl)methyl]sulfinyl]-1H-benzimidazole calcium salt and (-)-5-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole calcium salt.

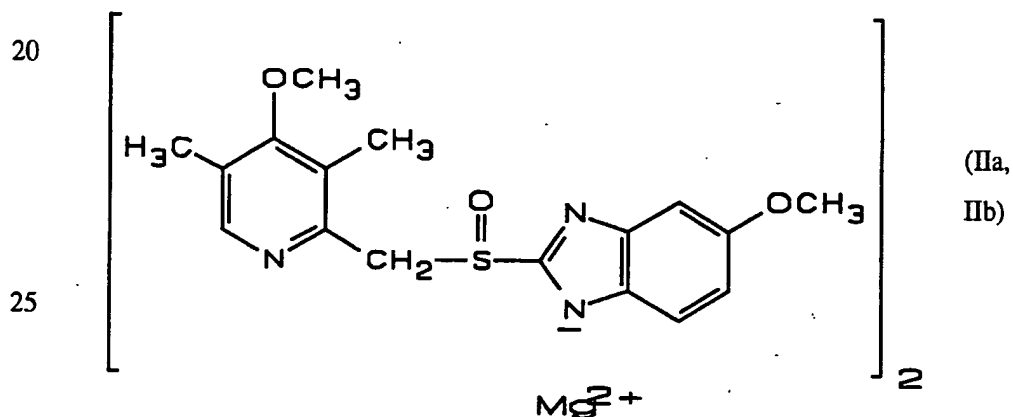
Most preferred salts according to the invention are the optically pure  $\text{Na}^+$  salts of omeprazole according to compounds Ia and Ib



Ia (+)-enantiomer

Ib (-)-enantiomer

and the optically pure magnesium salts of omeprazole according to compounds IIa and IIb



IIa (+)-enantiomer

IIb (-)-enantiomer

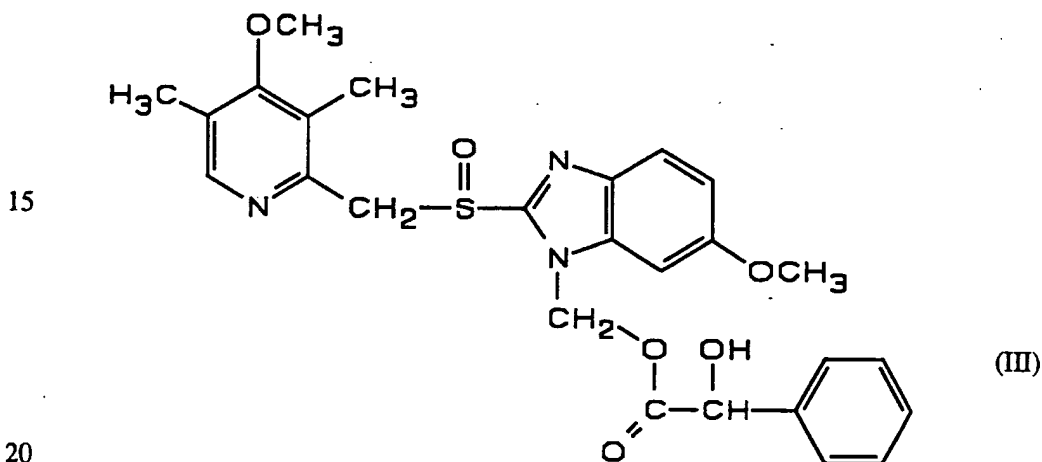
With the expression "optically pure Na<sup>+</sup> salts of omeprazole" is meant the (+)-enantiomer of omeprazole Na-salt essentially free of the (-)-enantiomer of omeprazole Na-salt and the (-)-enantiomer essentially free of the (+)-enantiomer, respectively. Single enantiomers of omeprazole have hitherto only been obtained as  
5 syrups and not as crystalline products. By means of the novel specific method according to one aspect of the invention of preparing the single enantiomers of omeprazole, the salts defined by the present invention are easy to obtain. In addition, the salts, however not the neutral forms, are obtained as crystalline products. Because it is possible to purify optically impure salts of the enantiomers  
10 of omeprazole by crystallisation, they can be obtained in very high optical purity, namely  $\geq 99.8\%$  enantiomeric excess (e.e.) even from an optically contaminated preparation. Moreover, the optically pure salts are stable towards racemization both in neutral pH and basic pH, which was surprising since the known deprotonation at the carbon atom between the pyridine ring and the chiral sulphur atom was  
15 expected to cause racemization under alkaline conditions. This high stability towards racemization makes it possible to use a single enantiomeric salt of the invention in therapy.

The specific method of preparation of the single enantiomers of omeprazole is a  
20 further aspect of the invention as mentioned above and it can be used to obtain the single enantiomers of omeprazole in neutral form as well as the salts thereof.

The compounds according to the invention may be used for inhibiting gastric acid secretion in mammals and man. In a more general sense, the compounds of the  
25 invention may be used for the treatment of gastric acid-related diseases and gastrointestinal inflammatory diseases in mammals and man, such as gastric ulcer, duodenal ulcer, reflux esophagitis, and gastritis. Furthermore, the compounds may be used for treatment of other gastrointestinal disorders where gastric antisecretory effect is desirable e.g. in patients on NSAID therapy, in patients with gastrinomas,  
30 and in patients with acute upper gastrointestinal bleeding. They may also be used

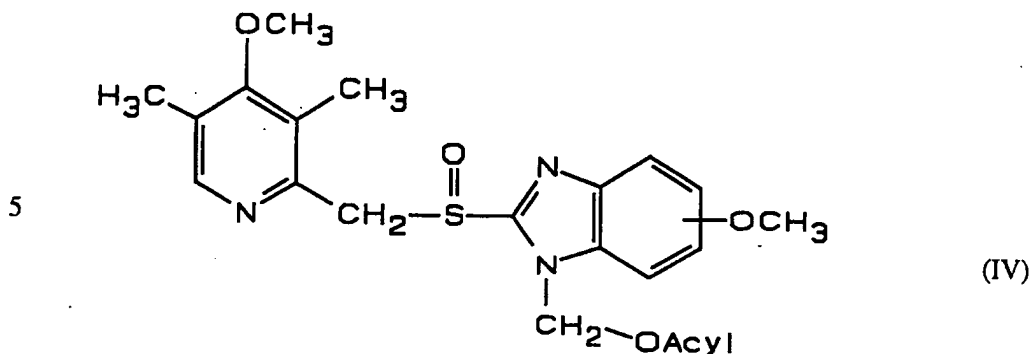
in patients in intensive care situations, and pre- and postoperatively to prevent acid aspiration and stress ulceration. The compound of the invention may also be used for treatment or prophylaxis of inflammatory conditions in mammals, including man, especially those involving lysozymal enzymes. Conditions that may be specifically mentioned are rheumatoid arthritis and gout. The compound of the invention may also be useful in the treatment of psoriasis as well as in the treatment of *Helicobacter* infections.

Yet a further aspect of the invention is the compound III, which is an intermediate used in the specific method of preparation.



### Preparation

The optically pure compounds of the invention, i.e. the single enantiomers, are prepared by separating the two stereoisomers of a diastereomeric mixture of the following type, 5- or 6-methoxy-2-[[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1-[acyloxymethyl]-1H-benzimidazole, formula IV



- 10 wherein the methoxy substituent in the benzimidazole moiety is in position 5 or 6,  
and wherein the Acyl radical is as defined below, followed by a solvolysis of each  
separated diastereomer in an alkaline solution. The formed single enantiomers of  
omeprazole are then isolated by neutralizing aqueous solutions of the salts of the  
single enantiomers of omeprazole with a neutralizing agent which can be an acid or  
15 an ester such as methyl formate.

The Acyl moiety in the diastereomeric ester may be a chiral acyl group such as  
mandeloyl, and the asymmetric center in the chiral acyl group can have either R or  
S configuration.

20

The diastereomeric esters can be separated either by chromatography or fractional  
crystallization.

- 25 The solvolysis usually takes place together with a base in a protic solvent such as  
alcohols or water, but the acyl group may also be hydrolysed off by a base in an  
aprotic solvent such as dimethylsulfoxide or dimethylformamide. The reacting base  
may be  $\text{OH}^-$  or  $\text{R}^1\text{O}^-$  where  $\text{R}^1$  can be any alkyl or aryl group.

- 30 To obtain the optically pure  $\text{Na}^+$  salts of the invention, i.e. the single enantiomers  
of omeprazole  $\text{Na}^+$  salts, the resulting compound is treated with a base, such as



NaOH, in an aqueous or nonaqueous medium, or with  $\text{NaOR}^2$  wherein  $\text{R}^2$  is an alkyl group containing 1-4 carbon atoms, or with  $\text{NaNH}_2$ . Also alkaline salts wherein the cation is  $\text{Li}^+$  or  $\text{K}^+$  may be prepared using lithium or potassium salts of the above mentioned bases. In order to obtain the crystalline form of the  $\text{Na}^+$  salt, addition of NaOH in a non-aqueous medium such as a mixture of 2-butanone and toluene, is preferred.

To obtain the optically pure  $\text{Mg}^{2+}$  salts of the invention, optically pure  $\text{Na}^+$  salts are treated with an aqueous solution of an inorganic magnesium salt such as  $\text{MgCl}_2$ , whereupon the  $\text{Mg}^{2+}$  salts are precipitated. The optically pure  $\text{Mg}^{2+}$  salts may also be prepared by treating single enantiomers of omeprazole with a base, such as  $\text{Mg}(\text{OR}^3)_2$ , wherein  $\text{R}^3$  is an alkyl group containing 1-4 carbon atoms, in a non-aqueous solvent such as alcohol (only for alcoholates), e.g. ROH, or in an ether such as tetrahydrofuran. In an analogous way, also alkaline salts wherein the cation is  $\text{Ca}^{2+}$  can be prepared, using an aqueous solution of an inorganic calcium salt such as  $\text{CaCl}_2$ .

Alkaline salts of the single enantiomers of the invention are, as mentioned above, beside the sodium salts (compounds Ia and Ib) and the magnesium salts (compound IIa and IIb), exemplified by their salts with  $\text{Li}^+$ ,  $\text{K}^+$ ,  $\text{Ca}^{2+}$  and  $\text{N}^+(\text{R})_4$ , where R is an alkyl with 1-4 C-atoms.

For clinical use the single enantiomers, i.e. the optically pure compounds, of the invention are formulated into pharmaceutical formulations for oral, rectal, parenteral or other modes of administrations. The pharmaceutical formulations contain the single enantiomers of the invention normally in combination with a pharmaceutically acceptable carrier. The carrier may be in form of a solid, semi-solid or liquid diluent, or capsule. These pharmaceutical preparations are a further object of the invention. Usually the amount of active compound is between 0.1-95% by weight of the preparation, between 0.2-20% by weight in preparations for

parenteral use and between 1-50% by weight in preparations for oral administration.

- 5 In the preparation of pharmaceutical formulations in form of dosage units for oral administration the optically pure compound may be mixed with a solid, powdered carrier, such as lactose, saccharose, sorbitol, mannitol, starch, amylopectin, cellulose derivates, gelatin or another suitable carrier, stabilizing substances such as alkaline compounds e.g. carbonates, hydroxides and oxides of sodium, potassium, calcium, magnesium and the like as well as with lubricating agents such as
- 10 magnesium stearate, calcium stearate, sodium stearyl fumarate and polyethylenglycol waxes. The mixture is then processed into granules or pressed into tablets. Granules and tablets may be coated with an enteric coating which protects the active compound from acid catalysed degradation as long as the dosage form remains in the stomach. The enteric coating is chosen among
- 15 pharmaceutically acceptable enteric-coating materials e.g. beeswax, shellac or anionic film-forming polymers and the like, if preferred in combination with a suitable plasticizer. To the coating various dyes may be added in order to distinguish among tablets or granules with different amounts of the active compound present.
- 20
- Soft gelatine capsules may be prepared with capsules containing a mixture of the active compound, vegetable oil, fat, or other suitable vehicle for soft gelatine capsules. Soft gelatine capsules may also be enteric-coated as described above.
- 25 Hard gelatine capsules may contain granules or enteric-coated granules of the active compound. Hard gelatine capsules may also contain the active compound in combination with a solid powdered carrier such as lactose, saccharose, sorbitol, mannitol, potato starch, amylopectin, cellulose derivates or gelatin. The capsules may be enteric-coated as described above.

30

Dosage units for rectal administration may be prepared in the form of suppositories which contain the active substance mixed with a neutral fat base, or they may be prepared in the form of a gelatine rectal capsule which contains the active substance in a mixture with a vegetable oil, paraffin oil or other suitable vehicle for gelatine rectal capsules, or they may be prepared in the form of a ready-made micro enema, or they may be prepared in the form of a dry micro enema formulation to be reconstituted in a suitable solvent just prior to administration.

Liquid preparation for oral administration may be prepared in the form of syrups or suspensions, e.g. solutions or suspensions containing from 0.2% to 20% by weight of the active ingredient and the remainder consisting of sugar or sugar alcohols and a mixture of ethanol, water, glycerol, propylene glycol and/or polyethylene glycol. If desired, such liquid preparations may contain colouring agents, flavouring agents, saccharine and carboxymethyl cellulose or other thickening agents. Liquid preparations for oral administration may also be prepared in the form of dry powder to be reconstituted with a suitable solvent prior to use.

Solutions for parenteral administrations may be prepared as solutions of the optically pure compounds of the invention in pharmaceutically acceptable solvents, preferably in a concentration from 0.1 to 10% by weight. These solutions may also contain stabilizing agents and/or buffering agents and may be manufactured in different unit dose ampoules or vials. Solutions for parenteral administration may also be prepared as dry preparations to be reconstituted with a suitable solvent extemporaneously before use.

The typical daily dose of the active compound will depend on various factors such as for example the individual requirement of each patient, the route of administration and the disease. In general, oral and parenteral dosages will be in the range of 5 to 500 mg per day of active substance.

The invention is illustrated by the following examples.

Example 1. Preparation of (+)-5-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole sodium salt

5  
100 mg (0.3 mmol) of (-)-5-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole (contaminated with 3% of the (+)-isomer) was dissolved in 1 ml of 2-butanone with stirring. 60 µl of an aqueous solution of 5.0 M sodium hydroxide and 2 ml of toluene were added. The resultant mixture was  
10 non-homogeneous. In order to obtain a clear solution, more 2-butanone was added (ca 1 ml) and the mixture was stirred at ambient temperature over night. The formed precipitate was filtered off and washed with ether. There was obtained 51 mg (46%) of the title compound as white crystals m.p. (decomposition) 246-248°C. The optical purity (e.e.) which was analyzed by chiral column chromatography was  
15 ≥99.8%.  $[\alpha]_D^{20} = +42,8^\circ$  (c=0.5%, water).

NMR data are given below.

20 Example 2. Preparation of (-)-5-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole sodium salt

100 mg (0.3 mmol) of (+)-5-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole (contaminated with 3% of the (-)-isomer) was  
25 dissolved in 1 ml of 2-butanone with stirring. 60 µl of an aqueous solution of 5.0 M sodium hydroxide and 2 ml of toluene were added. The resultant mixture was non-homogeneous. In order to obtain a clear solution, more 2-butanone was added (ca 1 ml) and the mixture was stirred at ambient temperature over night. The formed precipitate was filtered off and washed with ether. There was obtained 56  
30 mg (51%) of the title compound as white crystals m.p. (decomposition) 247-249°C.

The optical purity (e.e.) which was analyzed by chiral column chromatography was  $\geq 99.8\%$ .  $[\alpha]_D^{20} = -44.1^\circ$  (c=0.5%, water).

NMR data are given below.

5

Example 3. Preparation of (+)-5-methoxy-2-[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole magnesium salt

2.9 ml of a 0.1 M solution of NaOH was added to 0.10 g (0.29 mmol) (+)-5-methoxy-2-[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole. To this mixture 2 ml methylene chloride was added, and after mixing in a separatory funnel the aqueous solution was separated off. A solution of 14 mg (0.145 mmol)  $MgCl_2$  in water was added dropwise. The formed precipitate was isolated by centrifugation, and 52 mg (50%) of the product was isolated as an amorphous powder. The optical purity (e.e.) was 98%, and thus the same as the starting material. The optical purity was determined by chromatography on an analytical chiral column.  $[\alpha]_D^{20} = +101.2^\circ$  (c=1%, methanol). The Mg content of the sample was found to be 3.0%, shown by atomic absorption spectroscopy.

20

Example 4. Preparation of (-)-5-methoxy-2-[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole magnesium salt

(-)-5-methoxy-2-[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole sodium salt (0.500 g, 1.36 mmol) was dissolved in water (10 ml). To this mixture 10 ml of an aqueous solution of  $MgCl_2 \cdot xH_2O$  (138 mg, 0.68 mmol) was added dropwise and the formed precipitate was isolated by centrifugation. There was obtained 418 mg (86%) of the product as a white powder. The optical purity (ee) of the product was 99.8% which was the same as the optical purity of the starting material. The optical purity was determined by

30

chromatography on an analytical chiral column.  $[\alpha]_D^{20} = +129.9^\circ$  (c=1%, methanol).

Example 5. Preparation of (-)-5-methoxy-2-[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole magnesium salt

5 (+)-5-methoxy-2-[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-sulfinyl]-1H-benzimidazole sodium salt (0.165 g, 0.45 mmol) was dissolved in water (3 ml). To this mixture 2 ml of an aqueous solution of  $MgCl_2 \cdot xH_2O$  (46 mg, 0.23 mmol) was added dropwise and the formed precipitate was isolated by centrifugation. There  
10 was obtained 85 mg (51%) of the product as a white powder. The optical purity ( $ee$ ) of the product was 99.9% which was the same or better as the optical purity of the starting material. The optical purity was determined by chromatography on an analytical chiral column.  $[\alpha]_D^{20} = -128.2^\circ$  (c=1%, methanol).

15 Table 1

<u>Ex.</u>	<u>Solvent</u>	<u>NMR data <math>\delta</math> ppm</u>
20 1.	DMSO- $d_6$ 500 MHz	2.20 (s, 3H), 2.22 (s, 3H), 3.69 (s, 3H), 3.72 (s, 3H), 4.37 (d, 1H), 4.75 (d, 1H), 6.54 (dd, 1H), 6.96 (d, 1H) 7.30 (d, 1H), 8.21 (s, 1H).
25 2.	DMSO- $d_6$ 500 MHz	2.20 (s, 3H), 2.22 (s, 3H), 3.69 (s, 3H), 3.72 (s, 3H), 4.38 (d, 1H), 4.73 (d, 1H), 6.54 (dd, 1H), 6.96 (d, 1H), 7.31 (d, 1H), 8.21 (s, 1H).

Preparation of the synthetic intermediates according to the invention will be described in the following examples.

Example 6. Preparation of 6-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-(R/S)-sulfinyl]-1-[(R)-mandeloyloxymethyl]-1H-benzimidazole

A solution of 3.4 g sodium hydroxide in 40 ml water was added to a mixture of  
5 14.4 g (42 mmol) tetrabutylammonium hydrogen sulphate and 6.4 g (42 mmol)  
(R)-(-)-mandelic acid. The mixture was extracted with 400 ml chloroform. After  
separation, the organic extract was heated to reflux with 16.6 g (42 mmol) of the  
racemate of 6-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-sulfinyl]-  
1-[chloromethyl]-1H-benzimidazole. Evaporation of the solvent was followed by  
10 dilution with 100 ml dichloromethane and 700 ml ethyl acetate. The mixture was  
washed with 3 x 200 ml water and the organic solution was dried over MgSO<sub>4</sub> and  
then evaporated. The crude material was purified by recrystallization from 100 ml  
acetonitrile, giving 8.1 g of the title compound (38%) as a diastereomeric mixture.

15 NMR data are given below.

Example 7. Separation of the more hydrophilic diastereomer of 6-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-(R/S)-sulfinyl]-1-[(R)-mandeloyloxymethyl]-1H-benzimidazole

20

The diastereomers of the title compound in Example 6 were separated using  
reversed phase chromatography (HPLC). Approximately 300 mg of the  
diastereomeric mixture was dissolved in 10 ml hot acetonitrile which was diluted  
with 10 ml of a mixture of aqueous 0.1 M ammoniumacetate and acetonitrile  
25 (70/30). The solution was injected to the column and the compounds were eluted  
with a mixture of aqueous 0.1 M ammoniumacetate and acetonitrile (70/30). The  
more hydrophilic isomer was easier to obtain pure than the less hydrophilic one.  
The work up procedure for the fraction which contained pure isomer was as  
follows; extraction with dichloromethane, washing the organic solution with  
30 aqueous 5 % sodium hydrogen carbonate solution, drying over Na<sub>2</sub>SO<sub>4</sub> and

evaporation of the solvent on a rotavapor (at the end of the evaporation the removal of acetonitrile was facilitated by adding more dichloromethane). Using 1.2 g of the diastereomeric mixture with the above mentioned technique, the more hydrophilic isomer, 410 mg, was obtained in a pure state as a colourless syrup.

5

NMR data are given below.

Example 8. Preparation of 6-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-(R/S)-sulfinyl]-1-[(S)-mandeloyloxymethyl]-1H-benzimidazole

10

The product was obtained from 8.1 g (202 mmol) sodium hydroxide in 100 ml water, 34.4 g (101 mmol) tetrabutylammonium hydrogen sulfate, 15.4 g (101 mmol) (S)-(+)-mandelic acid and 39.9 g (101 mmol) of the racemate of 6-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-sulfinyl]-1-[chloromethyl]-1H-benzimidazole using the same procedure as in Example 6. Recrystallization from 100 ml acetonitrile yielded 21.3 g, i.e. 41% of the title compound as a diastereomeric mixture.

15

NMR data are given below.

20

Example 9. Separation of the more hydrophilic diastereomer of 6-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-(R/S)-sulfinyl]-1-[(S)-mandeloyloxymethyl]-1H-benzimidazole

25 The diastereomers of the title compound in Example 8 were separated using reversed phase chromatography (HPLC) in the same way as in Example 7, but using the diastereomeric mixture of 6-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-(R/S)-sulfinyl]-1-[(S)-mandeloyloxymethyl]-1H-benzimidazole instead of the (R)-mandelic ester used in Example 7. Using 2.1 g of the  
30 diastereomeric mixture, the more hydrophilic isomer, 760 mg, was obtained in a



pure state as a colourless syrup.

NMR data are given below.

5    Example 10. Preparation of (-)-5-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-sulfinyl]-1H-benzimidazole

0.23 g (0.45 mmol) of the more hydrophilic diastereomer of 6-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1-[(R)-mandeloyloxymethyl]-1H-benzimidazole was dissolved in 15 ml methanol. A solution of 36 mg (0.9 mmol) sodium hydroxid in 0.45 ml water was added, and after 10 minutes the mixture was evaporated on a rotavapor. The residue was partitioned between 15 ml water and 15 ml dichloromethane. The organic solution was extracted with 15 ml water and to the combined aqueous solutions was added 85 µl (1.4 mmol) methyl formate. After 15 minutes the mixture was extracted with 3x10 ml dichloromethane. The organic solution was dried over Na<sub>2</sub>SO<sub>4</sub> and then evaporated. There was obtained 0.12 g (77%) of the title compound as a colourless syrup. The optical purity (e.e.) which was analyzed by chiral column chromatography was 94%.  $[\alpha]_D^{20} = -155^\circ$  (c=0.5%, chloroform).

20

NMR data are given below

25    Example 11. Preparation of (+)-5-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-sulfinyl]-1H-benzimidazole

0.76 g (1.5 mmol) of the more hydrophilic diastereomer of 6-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1-[(S)-mandeloyloxymethyl]-1H-benzimidazole was dissolved in 50 ml methanol. A solution of 0.12 mg (3.0 mmol) sodium hydroxid in 1.5 ml water was added, and after 10 minutes the mixture was evaporated on a rotavapor. The residue was partitioned between 25 ml water and

30

25 ml dichloromethane. The organic solution was extracted with 25 ml water and to the combined aqueous solutions was added 200  $\mu$ l (3.2 mmol) methyl formate. After 15 minutes the mixture was extracted with 3x25 ml dichloromethane. The organic solution was dried over  $\text{Na}_2\text{SO}_4$  and then evaporated. There was obtained  
 5 0.42 g (81%) of the title compound as a colourless syrup. The optical purity (e.e.) which was analyzed by chiral column chromatography was 98%.  $[\alpha]_{\text{D}}^{20} = +157^\circ$  (c=0.5%, chloroform).

NMR data are given below

10

Table 2.

<u>Ex.</u>	<u>Solvent</u>	<u>NMR data <math>\delta</math> ppm</u>
6.	$\text{CDCl}_3$	2.18 (s, 3H), 2.20 (s, 3H), 2.36 (s, 3H), 2.39 (s, 3H),
15	500 MHz	3.77 (s, 3H), 3.78 (s, 3H), 3.82 (s, 3H), 3.87 (s, 3H), 4.80 (d, 1H), 4.88 (d, 1H), 5.0 (m, 2H), 5.34 (s, 2H), 6.43 (d, 1H), 6.54 (d, 1H), 6.6-6.7 (m, 2H), 6.90 (d, 1H), 6.95-6.98 (m, 2H), 7.01 (d, 1H), 7.2-7.3 (m, 6H), 7.37 (m, 2H), 7.44 (m, 2H), 7.58 (d, 1H), 7.62 (d, 1H), 7.95 (s, 1H), 7.97 (s, 1H).
7.	$\text{CDCl}_3$	2.20 (s, 3H), 2.36 (s, 3H), 3.78 (s, 3H), 3.82 (s, 3H),
20	500 MHz	4.80 (d, 1H), 5.00 (d, 1H), 5.35 (d, 1H), 6.43 (d, 1H), 6.63 (d, 1H), 6.90 (d, 1H), 6.97 (dd, 1H), 7.2-7.3 (m, 3H), 7.37 (m, 2H), 7.62 (d, 1H), 7.97 (s, 1H).
8.	$\text{CDCl}_3$	2.19 (s, 3H), 2.20 (s, 3H), 2.36 (s, 3H), 2.39 (s, 3H), 3.77
25	500 MHz	(s, 3H), 3.78 (s, 3H), 3.83 (s, 3H), 3.87 (s, 3H), 4.80 (d, 1H), 4.88 (d, 1H), 5.0 (m, 2H), 5.34 (s, 2H), 6.43 (d, 1H), 6.54 (d, 1H), 6.6-6.7 (m, 2H), 6.90 (d, 1H), 6.96-6.98 (m, 2H), 7.01
30		(d, 1H), 7.2-7.3 (m, 6H), 7.37 (m, 2H), 7.44 (m, 2H), 7.58 (d,

1H), 7.62 (d, 1H), 7.95 (s, 1H), 7.97 (s, 1H).

9.  $\text{CDCl}_3$  2.20 (s, 3H), 2.36 (s, 3H), 3.78 (s, 3H), 3.82 (s, 3H), 4.80  
500 MHz (d, 1H), 5.00 (d, 1H), 5.35 (d, 1H), 6.43 (d, 1H), 6.63  
5 (d, 1H), 6.90 (d, 1H), 6.97 (dd, 1H), 7.2-7.3 (m, 3H), 7.37  
(m, 2H), 7.62 (d, 1H), 7.97 (s, 1H).
10.  $\text{CDCl}_3$  2.18, (s, 3H), 2.22 (s, 3H), 3.68 (s, 3H), 3.83 (s, 3H),  
300 MHz 4.77 (m, 2H), 6.93 (dd, 1H),  $\approx 7.0$  (b, 1H),  $\approx 7.5$  (b, 1H), 8.19  
10 (s, 1H).
11.  $\text{CDCl}_3$  2.21 (s, 3H), 2.23 (s, 3H), 3.69 (s, 3H), 3.84 (s, 3H), 4.76 (m,  
2H), 6.94 (dd, 1H),  $\approx 7.0$  (b, 1H),  $\approx 7.5$  (b, 1H), 8.20 (s, 1H).

- 15 The best mode of carrying out the invention known at present is to use the sodium salts of the optically pure compounds of the invention, thus the compounds described in Example 1 and Example 2.

- 20 Pharmaceutical preparations containing the compounds of the invention as active ingredient are illustrated in the following formulations.

#### Syrup

- 25 A syrup containing 1% (weight per volume) of active substance was prepared from the following ingredients:

Compound according to Example 2	1.0 g
Sugar, powder	30.0 g
Saccharine	0.6 g
30 Glycerol	5.0 g

Flavouring agent	0.05 g
Ethanol 96%	5.0 g
Distilled water q.s. to a final volume of	100 ml

- 5 Sugar and saccharine were dissolved in 60 g of warm water. After cooling the active compound was added to the sugar solution and glycerol and a solution of flavouring agents dissolved in ethanol were added. The mixture was diluted with water to a final volume of 100 ml.

10 Enteric-coated tablets

An enteric coated tablet containing 50 mg of active compound was prepared from the following ingredients:

15	I	Compound according to Example 3 as Mg salt	500 g
		Lactose	700 g
		Methyl cellulose	6 g
20		Polyvinylpyrrolidone cross-linked	50 g
		Magnesium stearate	15 g
		Sodium carbonate	6 g
		Distilled water	q.s.
25	II	Cellulose acetate phthalate	200 g
		Cetyl alcohol	15 g
		Isopropanol	2000 g
		Methylene chloride	2000 g

- 30 I Compound according to Example 3, powder, was mixed with lactose and

granulated with a water solution of methyl cellulose and sodium carbonate. The wet mass was forced through a sieve and the granulate dried in an oven. After drying the granulate was mixed with polyvinylpyrrolidone and magnesium stearate. The dry mixture was pressed into tablet cores (10 000 tablets), each tablet  
5 containing 50 mg of active substance, in a tableting machine using 7 mm diameter punches.

II A solution of cellulose acetate phthalate and cetyl alcohol in  
10 isopropanol/methylene chloride was sprayed onto the tablets I in an Accela Cota<sup>R</sup>, Manesty coating equipment. A final tablet weight of 110 mg was obtained.

Solution for intravenous administration

15 A parenteral formulation for intravenous use, containing 4 mg of active compound per ml, was prepared from the following ingredients:

Compound according to Example 2	4 g
Sterile water to a final volume of	1000 ml

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The active compound was dissolved in water to a final volume of 1000 ml. The solution was filtered through a 0.22 µm filter and immediately dispensed into 10 ml sterile ampoules. The ampoules were sealed.

25 Capsules

Capsules containing 30 mg of active compound were prepared from the following ingredients:

30 Compound according to Example 1	300 g
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	Lactose	700 g
	Microcrystalline cellulose	40 g
	Hydroxypropyl cellulose low-substituted	62 g
	Disodium hydrogen phosphate	2 g
5	Purified water	q.s.

The active compound was mixed with the dry ingredients and granulated with a solution of disodium hydrogen phosphate. The wet mass was forced through an extruder and spheronized and dried in a fluidized bed dryer.

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500 g of the pellets above were first coated with a solution of hydroxypropyl methylcellulose, 30 g, in water, 750 g, using a fluidized bed coater. After drying, the pellets were coated with a second coating as given below:

15 Coating solution:

	Hydroxypropyl methylcellulose phthalate	70 g
	Cetyl alcohol	4 g
	Acetone	200 g
20	Ethanol	600 g

The final coated pellets were filled into capsules.

#### Suppositories

25

Suppositories were prepared from the following ingredients using a welding procedure. Each suppository contained 40 mg of active compound.

	Compound according to Example 2	4 g
30	Witepsol H-15	180 g

The active compound was homogenously mixed with Witepsol H-15 at a temperature of 41° C. The molten mass was volume filled into pre-fabricated suppository packages to a net weight of 1.84 g. After cooling the packages were heat sealed. Each suppository contained 40 mg of active compound.

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Stability towards racemization at different pH:es

The stability of the optically pure compounds of the invention towards racemization has been measured at low concentrations in refrigerator in aqueous buffer solutions at pH 8, 9.3, 10 and 11.2. The stereochemical stability was measured by comparing the optical purity for the (-)-isomer of 5-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole in buffer solution immediately after dissolving and after several days. The measurement was performed by chromatography on an analytical chiral column. The surprising high stereochemical stability in alkaline conditions for the compounds of invention is exemplified by the fact that no racemization for the test compound was obtained at pH 11.2 even after 21 days. At pH 8, 9.3 and 10, the chemical degradation of the compound is more apparent which makes the racemization measurement more difficult to perform, however at none of these pH values a detectable racemization was obtained after 16 days.

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In another racemization experiment with the optically pure compounds of the invention, an aqueous phosphate buffer solution (pH=11) of the (+)-isomer of 5-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole ( $c=10^{-5}M$ ) was warmed for 26 hours at 37°C without any racemization at all being observed.

25

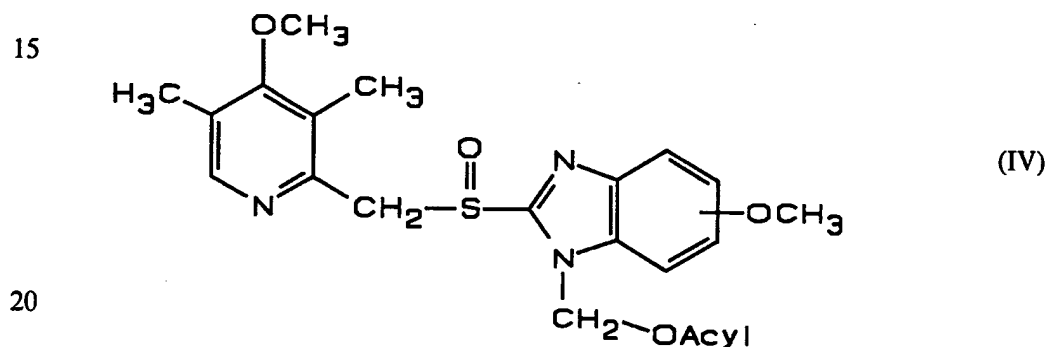
Claims

1. Optically pure compounds characterized in that the compounds are  $\text{Na}^+$ ,  $\text{Mg}^{2+}$ ,  $\text{Li}^+$ ,  $\text{K}^+$ ,  $\text{Ca}^{2+}$  and  $\text{N}^+(\text{R})_4$  salts of (+)-5-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole and (-)-5-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole, wherein R is an alkyl with 1-4 carbon atoms.
2. Compounds according to claim 1 characterized in that the compounds are (+)-5-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole sodium salt, (-)-5-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole sodium salt, (+)-5-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole magnesium salt, (-)-5-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole magnesium salt, (+)-5-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole calcium salt and (-)-5-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole calcium salt.
3. Compounds according to claims 1 and 2 characterized in that the compounds are (+)-5-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole sodium salt, (-)-5-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole sodium salt, (+)-5-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole magnesium salt and (-)-5-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole magnesium salt.
4. Compounds according to claims 1 and 2 characterized in that the compounds are (+)-5-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole sodium salt and (-)-5-methoxy-2-[[[4-methoxy-3,5-



dimethyl-2-pyridinyl)methyl]sulfinyl-1H-benzimidazole sodium salt in their crystalline forms.

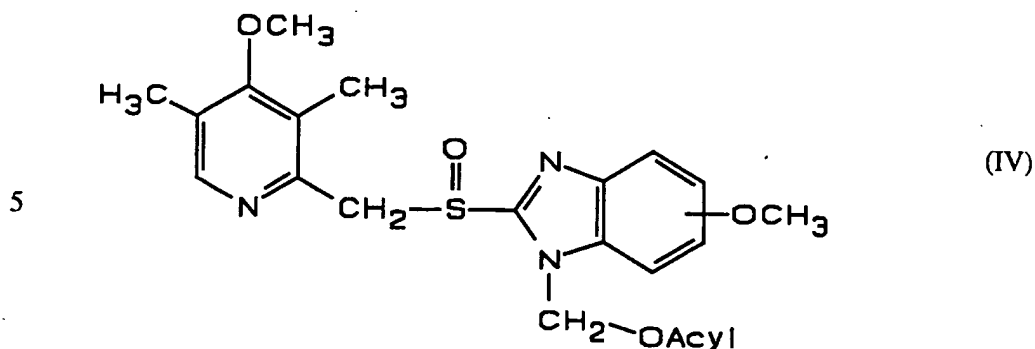
- 5 5. Compounds according to claims 1 and 2 characterized in that the compound is (+)-5-methoxy-2-[[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-sulfinyl-1H-benzimidazole sodium salt in its crystalline form.
6. Compounds according to claims 1 and 2 characterized in that the compound is (-)-5-methoxy-2-[[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-sulfinyl-1H-benzimidazole sodium salt in its crystalline form,
- 10 7. Process for the preparation of a compound according to claim 1 characterized in that a diastereomeric ester of formula IV



25 wherein Acyl designates a chiral acyl group such as mandeloyl, having either R or S configuration, is separated, and each of the separated diastereomers is dissolved in an alkaline solution where the acyloxymethyl group is hydrolyzed to give the optically pure compound.

- 30 8. Process according to claim 7 characterized in that the diastereomers are separated by chromatography or fractional crystallization.

9. Process according to claim 7 characterized in that the solvolysis is performed in alkaline solution consisting of a base in a protic solvent, such as alcohols or water; or a base in an aprotic solvent, such as dimethylsulfoxide or dimethylformamide.
10. Process for the preparation of a compound according to claim 1 in crystalline form characterized in that a product from the process in claim 7 is neutralized with a neutralizing agent which can be an acid or an ester such as methyl formate, followed by treatment with a base in non-aqueous solution.
11. Process for preparation of (+)-5-methoxy-2-[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-sulfinyl-1H-benzimidazole sodium salt and (-)-5-methoxy-2-[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl-1H-benzimidazole sodium salt in their crystalline forms characterized in that (+)-5-methoxy-2-[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-sulfinyl-1H-benzimidazole sodium salt and (-)-5-methoxy-2-[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl-1H-benzimidazole sodium salt crude product respectively is neutralized followed by treatment with NaOH in a non-aqueous medium.
12. Process for the preparation of (+)-5-methoxy-2-[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl-1H-benzimidazole and (-)-5-methoxy-2-[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl-1H-benzimidazole characterized in that a diastereomeric ester of formula IV



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wherein Acyl designates a chiral acyl group such as mandeloyl, having either R or S configuration, is separated, and each of the separated diastereomers is dissolved in an alkaline solution where the acyloxymethyl group is hydrolyzed off to give the optically pure compound after neutralization with a neutralizing agent which can be an acid or an ester.

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13. Process according to claim 12 characterized in that the diastereomers are separated by chromatography or fractional crystallization.

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14. Process according to claim 12 characterized in that the solvolysis is performed in alkaline solution consisting of a base in a protic solvent, such as alcohols or water; or a base in an aprotic solvent, such as dimethylsulfoxide or dimethylformamide.

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15. The compound (+)-5-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-sulfinyl]-1H-benzimidazole obtained by the process defined in claim 12.

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16. The compound (-)-5-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-sulfinyl]-1H-benzimidazole obtained by the process defined in claim 12.

17. Pharmaceutical preparation containing an optically pure compound according to any of claims 1-6 as active ingredient.
18. Optically pure compounds according to any of claims 1-6 for use in therapy.
- 5 19. Use of an optically pure compound according to any of claims 1-6 in the preparation of a pharmaceutical formulation for inhibiting gastric acid secretion.
- 10 20. Use of an optically pure compound according to any of claims 1-6 for the preparation of a pharmaceutical formulation for the treatment of gastrointestinal inflammatory diseases.
- 15 21. A method for inhibiting gastric acid secretion comprising administration to a mammal including man in need of such treatment an effective amount of an optically pure compound according to any of claims 1-6.
- 20 22. A method for the treatment of gastrointestinal inflammatory diseases comprising administration to a mammal including man in need of such treatment an effective amount of an optically pure compound according to any of claims 1-6.
23. The compound 6-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]-1-[mandeloyloxymethyl]-1H-benzimidazole.

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 94/00509

<b>A. CLASSIFICATION OF SUBJECT MATTER</b>		
IPC5: C07D 401/12, A61K 31/44 According to International Patent Classification (IPC) or to both national classification and IPC		
<b>B. FIELDS SEARCHED</b>		
Minimum documentation searched (classification system followed by classification symbols)		
IPC5: C07D		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
SE,DK,FI,NO classes as above		
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)		
CAS-ONLINE		
<b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b>		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP, A2, 0124495 (AKTIEBOLAGET HÄSSLE), 7 November 1984 (07.11.84)  --	1-6,11,15-20
Y	DE, A1, 4035455 (BYK GULDEN LOMBERG CHEMISCHE FABRIK GMBH), 14 May 1992 (14.05.92)	1-6,11,15-20
X	-- -----	7-10,12-14, 23
<input type="checkbox"/> Further documents are listed in the continuation of Box C. <input checked="" type="checkbox"/> See patent family annex.		
* Special categories of cited documents: "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family		
Date of the actual completion of the international search		Date of mailing of the international search report
29 July 1994		17 -08- 1994
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86		Authorized officer  Göran Karlsson Telephone No. +46 8 782 25 00

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 94/00509

## Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 21-22  
because they relate to subject matter not required to be searched by this Authority, namely:  
A method for treatment of the human or animal body by therapy, see rule 39.1(iv).
2. ☐ Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.  
☐ No protest accompanied the payment of additional search fees.

## INTERNATIONAL SEARCH REPORT

Information on patent family members

02/07/94

International application No.

PCT/SE 94/00509

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A2- 0124495	07/11/84	SE-T3- 0124495	
		AU-B- 563842	23/07/87
		AU-A- 2525784	06/09/84
		CA-A- 1264751	23/01/90
		GB-A,B- 2137616	10/10/84
		JP-C- 1651336	30/03/92
		JP-B- 3013233	22/02/91
		JP-A- 59167587	21/09/84
		SU-A- 1314953	30/05/87
		US-A- 4738974	19/04/88
DE-A1- 4035455	14/05/92	AU-A- 8840691	11/06/92
		WO-A- 9208716	29/05/92